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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,533	05/26/2005	David J. Waxman	701586-52522	1019

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EXAMINER	
NGUYEN, QUANG	

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,533	WAXMAN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *20,22,25-28,34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21,23,24 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/23/04;5/29/07;1/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-36 are pending in the present application.

Applicant's election of Group I, drawn to a method of prolonging expression of heterologous gene encoding a prodrug activating enzyme, in the reply filed on 7/10/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant further elected the following species: (a) p35 as a species of apoptosis inhibiting agent; (b) cytochrome P450 as a species of a pro-drug activating enzyme; (c)) cyclophosphamide and other P450 prodrugs including bioreductive agents activated by P450 and/or NADPH-P450 reductase as a species of the prodrug; (d) p53 as a species of a factor promoting apoptosis; and (e) Trail as a species of a death receptor ligand.

It is noted that Applicants fail to further elect a species of the prodrug-activating cytochrome P450 enzyme as recited in the Markush of claim 10 as required in the Office Action mailed on 6/8/07 (pages 5-6). However, upon further consideration this species restriction is withdrawn.

Claims 20, 22, 25-26 and 34-35 are withdrawn from further consideration because they are directed to non-elected inventions. Claims 27-28 and 36 were also withdrawn from further consideration because they are directed to non-elected species for an apoptosis inhibiting agent.

Accordingly, claims 2-18, 31-33 and linking claims 1, 19, 21, 23-24 and 29-30 are examined on the merits herein with the elected invention and above elected species.

Claim Objections

Claim 24 is objected to because of the phrase "said nucleic acid encoding and apoptosis inhibiting agent" on line 7 of the claim. It appears that the term "and" in this phrase is inadvertently misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 19, 21 and 23-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Bilbao et al. (WO 99/55382).

Bilbao et al disclose at least a method to prolong or enhance transgene expression (up to 2 log increase), including a therapeutic transgene expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, due to the

attenuation of expression of the transferred therapeutic gene based at least in part on loss of vector transduced cells in a variety of gene therapy applications (see at least the abstract; page 18, line 10 continues to line 3 of page 19; page 19, line 28 continues to line 5 of page 20; examples 26). Bilbao et al also teach specifically that at least a toxin gene has been selectively delivered for expression in cancer cells to achieve their eradication in a molecular chemotherapy approach (page 2, lines 15-27), and *in vivo* gene therapy approaches have been developed to treat metabolic and blood disorders, such as hemophilia, via *in vivo* gene transfer to the liver (page 4, lines 5-14). A toxin gene product to be expressed in cancer cells for their eradication can be considered to be a soluble therapeutic factor because it is synthesized and soluble within the tumor cell's internal environment. Bilbao et al further state that "Strategies to prolong the expression of transgenes delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility" (page 52, lines 6-10).

The teachings of Bilbao et al meet every limitation of the instant broad claims. Therefore, the reference anticipates the instant claims.

Claims 1, 19, 23-24, 29-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Wilson et al. (US 2002/0131961 A1).

Wilson et al already teach at least a method for gene transfer comprising the step of exposing a population of host cells in both *in vitro* and in a mammalian patient (e.g., hepatocytes, lung, muscle, epithelial cells) to a recombinant viral vector which

comprises a gene encoding an anti-apoptotic agent, a selected transgene, and regulatory sequences which control expression of said anti-apoptotic agent and said transgene or a first recombinant viral vector comprising a gene encoding an anti-apoptotic agent and a second recombinant viral vector comprising a selected transgene; and subsequently contacting the entire population of host cells with an apoptotic agent such as members of the tumor necrosis factor family, chemical reagents such s those conventionally used in chemotherapeutic regimen, against which Bcl-2 confers protection (see at least Summary of the Invention; paragraphs 26, 28, 56; and example 8). Wilson et al further teach that the recombinant viral vector replicates upon division of the cells which it transduces and is passed on to the progeny cells (paragraphs 24, 33), and that any anti-apoptotic agent can be selected including Bcl-2 (paragraph 25). Selected transgenes includes those encoding growth hormone, erythropoietin, factor IX, liver enzymes such as ornithine transcarbamylase, arginase and others (paragraphs 32, 110-111).

The teachings of Wilson et al meet every limitation of the instant broad claims. Therefore, the reference anticipates the instant claims.

Claims 1, 19 and 23-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Luo et al. (Human gene therapy 12:2191-2202, 2001; IDS).

Luo et al already teach a method in which Ad2/FasL/p35 reduced lumen stenosis and neointimal formation in rabbit models for balloon-injured femoral and iliac arteries, and that coexpression of p35 enhanced the inhibition of neointimal formation by Fas

ligand (see at least the abstract; and Materials and Methods section). A FasL gene product to be expressed in vascualar smooth muscle cells can be considered to be a soluble therapeutic factor because it is synthesized and soluble within the vascular smooth muscle cell's internal environment.

The teachings of Luo et al meet every limitation of the instant broad claims. Therefore, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13, 19, 21, 23-24 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382).

Waxman et al disclose methods of killing neoplastic cells in both *in vitro* and in a mammalian patient, including a human patient, using NADPH-cytochrome P450 reductase (RED) gene transfer in combination with cytochrome P450 gene transfer to enhance the sensitivity of neoplastic cells to anti-cancer drugs that are activated by P450 enzymes, wherein the P450 gene and the RED gene are delivered using one or more viral vectors (e.g., retrovirus, adenovirus, and others), the cytochrome P45 gene is a mammalian gene such as P450 1A1, 1A2, 1B1, 2B1, 2B2, 2B4 and others and the P450-activated chemotherapeutic agent is cyclophosphamide (CPA), ifosfamide (IFA) or any other P450-metabolized chemotherapeutic drug (See at least Summary of the Invention, pages 7-14; page 40, lines 27-30). Waxman et al further teach that the P450/RED gene therapy method may also be combined with other established cancer therapeutic genes, including tumor suppressor genes, such as p53, apoptotic factors, such as bax, tumor necrosis factor alpha, and caspases, and cytokines such as IL-2, IL-4 and IL-12 (page 12, first full paragraph). Waxman et al also teach targeting specificity for P450 and RED gene delivery is facilitated by "transcriptional targeting" including the use of tumor-specific or tumor-selective DNA enhancer sequences (page 12, second full paragraph; page 31, first full paragraph). Waxman et al also disclose that although the viral genomes of the viral vectors used in the methods should be modified to remove or limit their ability to replicate, however, replication conditional viruses are also useful

(page 33, line 27 continues to line 11 of page 34). Waxman et al also note that some therapeutic enhancement may also be anticipated in tumor cells with high levels of endogenous RED expression (page 55, lines 11-13); tumor cells transfected with both P450/RED genes (e.g., 9L/2B6/reducase cells) are themselves more chemosensitive and readily killed by CPA and IFA than others (see Fig. 15, and page 70, lines 12-13); current gene therapy technologies are limited by their inability to deliver prodrug activation or other therapeutic genes to a population of tumor cells with 100% efficiency and bystander cytotoxicity resultting when active drug metabolites diffuse or otherwise transferred from their site of generation within a transduced tumor cell to a neighboring, naïve tumor cell leads to significant tumor regression even when a minority of tumor cell is tranduced with the prodrug activation gene (page 3, lines 15-28).

Waxman et al do not teach methods of killing neoplastic cells further comprising the step of transducing neoplastic cells already transduced with a vector encoding a heterologous gene with a vector encoding an apoptosis inhibiting agent.

At the effective filing date of the present application, Bilbao et al already disclosed at least a method to prolong or enhance transgene expression (up to 2 log increase), including a therapeutic transgene expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, due to the attenuation of expression of the transferred therapeutic gene based at least in part on loss of vector transduced cells in a variety of gene therapy applications (see at least the abstract; page 18, line 10 continues to line 3 of page 19; page 19, line 28 continues to line 5 of page 20; examples

26). Bilbao et al also taught specifically that at least a toxin gene has been selectively delivered for expression in cancer cells to achieve their eradication in a molecular chemotherapy approach (page 2, lines 15-27). Bilbao et al further state that "Strategies to prolong the expression of transgenes delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility" (page 52, lines 6-10).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Waxman et al. by further comprising the step of transducing neoplastic cells already transduced with both P450/RED genes with a vector encoding an apoptosis inhibiting agent, such as Bcl-2, in light of the teachings of Bilbao et al.

An ordinary skilled artisan would have been motivated to carry out the above modification in order to achieve maximal intratumoral chemotherapeutic drug activation via enhanced expression levels of both P450/RED genes and/or a transient delayed in the death of tumor cells tranduced with both P450/RED genes to produce or generate a more prolonged and higher concentration of cytotoxic drug metabolites to neighboring native tumor cells, a bystander cytotoxicity, that is known to lead to significant tumor regression. Bilbao et al already demonstrated successfully a method to prolong or enhance transgene expression (up to 2 log increase), including a therapeutic transgene expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, and state specifically state that "Strategies to prolong the expression of

transgenes delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility".

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 14-18 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382) as applied to claims 1-13, 19, 21, 23-24 and 29-30 above, and further in view of Robertson et al (US 6,709,866) and Griffith et al. (US 6,900,185).

The combined teachings of Waxman et al. and Bilbao et al. were already presented above. However, none of the references teaches specifically the use of a vector comprising a nucleic acid encoding an apoptosis inhibiting agent operably linked to a regulatable promoter and/or further comprising a nucleic acid encoding a death receptor ligand, particularly Trail (the elected species) or a factor promoting apoptosis,, particularly p53 (elected species) expressed under control of a regulatable promoter, even though Waxman et al teach specifically that the P450/RED gene therapy method may also be combined with other established cancer therapeutic genes, including tumor suppressor genes, such as p53, apoptotic factors, such as bax, tumor necrosis factor alpha, and caspases, and cytokines.

However, at the effective filing date of the present application Robertson et al already taught at least the use of a recombinant viral vector expressing various anti-apoptotic polypeptides such as NAIP, HIAP, HIAP2, XIAP and other under the control of a regulatable promoter to inhibit death of a cell of the nervous system in a patient (see at least Summary of the Invention, particularly col. 3, lines 19-23; and cols. 20-22).

Additionally, Griffith et al already taught a method of inducing tumor cell apoptosis using Trail/Apo2-L gene transfer in a mammal, and optionally in combination with chemotherapeutic agents, radiotherapeutic agents or immune potentiating genes or proteins (see at least Summary of the Invention). Griffith et al further taught that Trail has an apparent unique ability to induce apoptosis in a wide range of transformed cell lines but not in normal tissues and cells (col. 1, lines 15-20). Griffith et al also disclosed that expression of Trail/Apo2-L gene is under the control of a promoter, including an inducible promoter or a tissue-specific promoter (col. 10, lines 1-16).

It would have been obvious for an ordinary skilled artisan to further modify the teachings of Waxman et al. and Bilbao et al., by also using a vector comprising a nucleic acid encoding an apoptosis inhibiting agent operably linked to a regulatable promoter and/or further comprising a nucleic acid encoding a death receptor ligand, particularly Trail (the elected species) or a factor promoting apoptosis,, particularly p53 (elected species) expressed under control of a regulatable promoter in light of the teachings of Robertson et al. and Bilbao et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because the expression of an antiapototic gene and/or an apopotic gene

under a regulatable promoter *in vivo* has been widely used and applied in various gene therapy applications as taught by Robertson et al. and Griffith et al. Additionally, the expression of a transgene under a regulatable promoter can be turned on or off as needed or required by the treated patients. Furthermore, an ordinary skilled artisan would also have been motivated to select Trail/Apo2-L gene transfer to treat a mammal having a cancer due to its apparent unique ability to induce apoptosis in a wide range of transformed cell lines but not in normal tissues and cells.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., Robertson et al.; Griffith et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-6 (with respect to the elected species p35) are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382) as applied to claims 1-13, 19, 21, 23-24 and 29-30 above, and further in view of Beidler et al. (J. Biol. Chem. 270:16526-16528, 1995).

The combined teachings of Waxman et al. and Bilbao et al. were already presented above. However, none of the references teaches specifically the use of a vector comprising a nucleic acid encoding an apoptosis inhibiting agent which is p35.

However, at the effective filing date of the present application Beidler et al. already taught that the baculovirus p35 protein is able to interrupt a highly conserved

and ubiquitous component of the death machinery because p35 inhibits TNF- and Fas-induced apoptosis, blocks the cleavage of PARP, a death substrate in the apoptotic pathway as well as blocking developmental, viral, and x-irradiation-induced cell death (see at least the abstract; page 16528, col. 1, last paragraph).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Waxman et al. and Bilbao et al., by also using a vector comprising a nucleic acid encoding an apoptosis inhibiting agent that is baculovirus p35 in light of the teachings of Beidler et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Beidler et al. already taught that the baculovirus p35 protein is able to interrupt a highly conserved and ubiquitous component of the death machinery.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., Beidler et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D.
PRIMARY EXAMINER